Variability In Parameter Values

Many factors affecting pharmacokinetic parameters should be considered when tailoring drug administration for a particular patient. Even with dosage adjustment, however, sufficient variability usually remains; thus, drug response and, in some cases, plasma drug concentration must be closely monitored.

Age and weight: For some drugs, the effects of age and weight on pharmacokinetics are well established. For persons aged 6 mo to 20 yr, renal function appears to correlate well with BSA. Thus, for drugs primarily eliminated unchanged by renal excretion, clearance in children varies with age according to change in BSA. For persons > 20 yr, renal function decreases about 1%/yr. Thus, dosage of these drugs can be adjusted by age. BSA also correlates with metabolic clearance in children, although exceptions are common. For newborns and infants, renal and hepatic functions are not fully developed, and generalizations, except for the occurrence of rapid change, are less accurate.

Renal function impairment: Renal clearance of most drugs appears to vary directly with creatinine clearance, regardless of which renal disease is present. The change in total clearance depends on the contribution of the kidneys to total elimination. Thus, total clearance should be proportional to renal function (creatinine clearance) for drugs excreted unchanged and to be unaffected for drugs eliminated by metabolism.

Renal failure may change the apparent volume of distribution, which decreases for digoxin because of decreased tissue binding and increases for phenytoin, salicylic acid, and many other drugs because of decreased binding to plasma proteins.

Physiologic stress: Concentration of the acute-phase protein α_1-acid glycoprotein increases during physiologic stress (eg, MI, surgery, ulcerative colitis, Crohn's disease). Consequently, the binding of several drugs (eg, propranolol, quinidine, disopyramide) to this protein increases, and the apparent volume of distribution of these drugs decreases accordingly.

Hepatic disease: Hepatic dysfunction can change metabolic clearance, but good correlates or predictors of the changes are unavailable. Hepatic cirrhosis can dramatically reduce drug metabolism and often results in reduced plasma protein binding because of

lowered plasma albumin. Acute hepatitis, with elevated serum enzymes, usually does not alter drug metabolism.

Other diseases: Heart failure, pneumonia, hyperthyroidism, and many other diseases ca alter the pharmacokinetics of drugs.

Drug interactions: Pharmacokinetic parameter values and, therefore, drug response may be affected by drug interactions. Most interactions are graded, and the extent of the interaction depends on the concentrations of both drugs. Thus, determining and adjusting drug dosage is difficult (see Drug Interactions in Ch. 301).

Dosage: In some instances, changes in dose, dosing rate, or duration of therapy alter a drug's kinetics. For example, as dose is increased, the bioavailability of griseofulvin decreases because of the drug's low solubility in the fluids of the upper GI tract. For phenytoin, steady-state plasma concentration increases disproportionately when dosing rat is increased, because the metabolizing enzyme has a limited capacity to eliminate the drug, and the usual dosing rate approaches the maximum rate of metabolism. Plasma carbamazepine concentration decreases during long-term use because carbamazepine induces its own metabolism. Other causes of dosage-dependent kinetic changes are saturable plasma protein and tissue binding (eg, phenylbutazone), saturable secretion in the kidneys (eg, high-dose penicillin), and saturable metabolism during the first pass through the liver (eg, propranolol).